



# ExpoApp: An integrated system to assess multiple personal environmental exposures

David Donaire-Gonzalez<sup>a,b</sup>, Antònia Valentín<sup>a</sup>, Erik van Nunen<sup>b</sup>, Ariadna Curto<sup>a</sup>, Albert Rodriguez<sup>c</sup>, Mario Fernandez-Nieto<sup>c</sup>, Alessio Naccarati<sup>d</sup>, Sonia Tarallo<sup>d</sup>, Ming-Yi Tsai<sup>e,f,i</sup>, Nicole Probst-Hensch<sup>e,f</sup>, Roel Vermeulen<sup>b</sup>, Gerard Hoek<sup>b</sup>, Paolo Vineis<sup>g</sup>, John Gulliver<sup>g,h</sup>, Mark J. Nieuwenhuijsen<sup>a,\*</sup>

<sup>a</sup> ISGlobal, Universitat Pompeu Fabra, CIBER Epidemiología y Salud Pública, Barcelona, Spain

<sup>b</sup> Institute for Risk Assessment Sciences (IRAS), Division of Environmental Epidemiology (EEPI), Utrecht University, Utrecht, the Netherlands

<sup>c</sup> Ateke Solutions, Barcelona 08940, Spain

<sup>d</sup> Italian Institute for Genomic Medicine (IIGM), Torino, Italy

<sup>e</sup> Swiss Tropical and Public Health Institute (TPH), Basel, Switzerland

<sup>f</sup> University of Basel, Basel, Switzerland

<sup>g</sup> MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College, London, UK

<sup>h</sup> Centre for Environmental Health and Sustainability, University of Leicester, UK

<sup>i</sup> Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, USA

## ARTICLE INFO

Handling Editor: Hanna Boogaard

### Keywords:

Personal exposure monitoring  
Ultrafine particles  
Inhalation  
Green spaces  
Microenvironments

## ABSTRACT

To assess environmental exposures at the individual level, new assessment methods and tools are required. We developed an exposure assessment system (ExpoApp) for smartphones. ExpoApp integrates: (i) geo-location and accelerometry measurements from a waist attached smartphone, (ii) data from portable monitors, (iii) geographic information systems, and (iv) individual's information. ExpoApp calculates time spent in microenvironments, physical activity level, inhalation rate, and environmental exposures and doses (e.g., green spaces, inhaled ultrafine particles- UFP). We deployed ExpoApp in a panel study of 158 adults from five cities (Amsterdam and Utrecht- the Netherlands, Basel- Switzerland, Norwich- UK, and Torino- Italy) with an UFP monitor. To evaluate ExpoApp, participants also carried a reference accelerometer (ActiGraph) and completed a travel-activity diary (TAD). System reliability and validity of measurements were evaluated by comparing the monitoring failure rate and the agreement on time spent in microenvironments and physical activity with the reference tools. There were only significant failure rate differences between ExpoApp and ActiGraph in Norwich. Agreement on time in microenvironments and physical activity level between ExpoApp and reference tools was 86.6% (86.5–86.7) and 75.7% (71.5–79.4), respectively. ExpoApp estimated that participants inhaled  $16.5 \times 10^{10}$  particles/day of UFP and had almost no contact with green spaces (24% of participants spent  $\geq 30$  min/day in green spaces). Participants with more contact with green spaces had higher inhaled dose of UFP, except for the Netherlands, where the relationship was the inverse. ExpoApp is a reliable system and provides accurate individual's measurements, which may help to understand the role of environmental exposures on the origin and course of diseases.

## 1. Introduction

Humans are exposed to lifelong environmental stressors (Wild, 2005). To date, most of the technological investments have focused on

the genome and have given the environment a secondary role (Wild, 2011). As a result, it has not been until the last decade that technology dedicated to personal environmental exposure has received more attention. Since > 70% of the origin of chronic non-communicable

**Abbreviations:** AC1, Gwet agreement coefficient; App, application; BMI, Body Mass Index; CCC, concordance correlation coefficient; EPA, Environmental Protection Agency; GIS, geographic information system; IQR, interquartile range; MET, Metabolic Equivalent Task; ONA, Optimized Noise reduction Averaging; Server, cloud server; TAD, Travel Activity Diary; UFP, ultrafine particles

\* Corresponding author at: ISGlobal, PRBB, Doctor Aiguader 88, 08003 Barcelona, Catalonia, Spain.

E-mail address: [mark.nieuwenhuijsen@isglobal.org](mailto:mark.nieuwenhuijsen@isglobal.org) (M.J. Nieuwenhuijsen).

<https://doi.org/10.1016/j.envint.2019.02.054>

Received 31 October 2018; Received in revised form 20 January 2019; Accepted 21 February 2019

0160-4120/ © 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

diseases remains without explanation (Rappaport, 2016), the development of affordable and accurate systems to assess personal environmental exposures is an urgent need that will shape the future of individual and public health interventions (Khoury et al., 2016).

Personal environmental exposures depend on the time, location, activity/behaviour, and surrounding environment of individuals (Nieuwenhuijsen et al., 2014; Nieuwenhuijsen et al., 2015). However, up to now, researchers have been experiencing serious difficulties in obtaining, directly or indirectly, spatiotemporal-resolved measures due to inconvenience and burden of current assessment methods. Consequently, most environmental studies have relied on ambient estimates (e.g., exposure based on participants' residential addresses) as predictors of individuals' exposures or have focused only on one exposure (Vineis et al., 2017; Vineis, 2004). This might have severely compromised the estimated risks associated with the exposures due to poor correlation between ambient and personal exposures (Nieuwenhuijsen et al., 2015), or the lack of control for concomitant exposures (Wild, 2005; Vineis, 2004). Therefore, as part of the EXPOsOMICS project (Vineis et al., 2017), we developed ExpoApp, an integrated system able to capture highly resolved information on time, location, activity, and personal exposures by taking advantage of recent technological advances in mobile personal computers, miniaturization of sensors, and geographic information systems (GIS) (Turner et al., 2017).

Here we (i) show the usefulness of ExpoApp for the integration, post-processing and visualization of multiple personal external exposures, (ii) compare its real-world measurements of time in microenvironments and physical activity level against reference tools, and (iii) describe ExpoApp estimates on time in-transit, physical activity, inhalation rate, ultrafine particle (UFP) exposure, UFP inhaled dose, and contact with green spaces in a European context.

## 2. Methods

The present study is part of the EXPOsOMICS project, which has been described in detail elsewhere (Vineis et al., 2017). Briefly, EXPOsOMICS aims to find the associations and disentangle the pathways between the external exposome and biological markers as measured through a range of omics technologies and relate these exposures and markers to health effects.

### 2.1. Introduction to ExpoApp

ExpoApp system in its current version combines: (i) geo-location and accelerometry measurements from a smartphone attached to the waist, (ii) air pollution measurements (e.g., UFP and black carbon) from portable monitors, (iii) green spaces from OpenStreetMap, and (iv) participants' information (detailed in Section 2.2). The system was developed by Ateknea Solutions, a technology center specialized in engineering and innovation (<http://www.ateknea.com>; e-mail: [info@ateknea.com](mailto:info@ateknea.com)), following the specifications of the EXPOsOMICS partners.

The system is composed of a cloud server (Server) and a smartphone application (App). The Server is designed for: (i) predefining and setting up the measurements to include in the exposure assessment through a Web portal (Fig. 1), (ii) backing up, integrating, and post-processing the measures (detailed in Section 2.2), and (iii) visualizing and downloading the personal exposure assessments (Fig. 2). The App is designed to get information from the smartphone built-in sensors (i.e. clock, satellite and network navigation systems, accelerometer, barometer, and screen status), as well as from wearable and portable sensors via Bluetooth 4.0 (Fig. 1). The App design minimizes the battery use by working as a background service, guarantees the confidentiality of the information collected using asymmetric encryption (128 bits), and prevents data loss through backing up locally and remotely.

### 2.2. ExpoApp data integration and post-processing

ExpoApp data integration includes: i) personal information of participants, ii) data from the built-in sensors of the smartphone and external sensors with Bluetooth 4.0, and iii) external data such as data from portable sensors without Bluetooth 4.0 and diaries. The required personal information of participants includes age, gender, weight, and home and work addresses, which is manually added through the web portal by researchers. The data from the built-in sensors of the smartphone and external sensors with Bluetooth 4.0 are transferred through the smartphone to Server automatically using a secure encrypted communication protocol every time that the smartphone is plugged and has access to Wi-Fi. The data from portable sensors without Bluetooth 4.0 can be uploaded to ExpoApp manually by researchers. Currently, ExpoApp is able to integrate data from the UFP monitor DISCmini (Matter-Aerosol; Wohlen, Switzerland), the black carbon monitor MicroAeth (model AE51, AethLabs; San Francisco, USA), and time-resolved travel-activity diaries (TAD). However, the system can be easily adapted to include other monitors such as noise monitors. Once data are in ExpoApp system, they are backed-up into a study-specific folder, being only accessible to the study staff.

Currently, data post-processing is applied to the measures of geo-location, accelerometry, UFP, and black carbon. The measures of geo-location are post-processed to determine time spent in microenvironments (home, work, in-transit, and others) and green spaces. To obtain time spent in microenvironments, ExpoApp uses participants' home and work addresses and a validated map-matching algorithm for travel-activity location (Donaire-Gonzalez et al., 2016). To obtain time spent in green spaces, ExpoApp overlays each smartphone geo-location over the OpenStreetMap (<https://www.openstreetmap.org>), following the methodology of Triguero et al study (see Supporting information) (Triguero-Mas et al., 2017).

The accelerometry measures are post-processed to determine smartphone/belt wearing intervals (i.e. time wearing the smartphone attached to the waist with ExpoApp turned on), intensity of physical activity (METs- Metabolic Equivalent Task), and inhalation rate (L). The current post-processing algorithms of accelerometry measurements require that the smartphone has to be worn on a belt attached to the waist. ExpoApp accelerometry measures are converted to ActiGraph counts by applying the acceleration-to-count equation [ $\text{Vertical Acceleration} \geq 0.27$  count =  $-48.08 + 211.81 * \text{Vertical Acceleration}^{0.95}$ ;  $\text{Vertical Acceleration} < 0.27$  count = 0]. This equation is specific for the accelerometer in the Samsung Galaxy S3 used in this study (LSM330DLC 3-axis) and has been developed following the methodology described in detail elsewhere (Donaire-Gonzalez et al., 2013). The smartphone/belt wearing intervals and intensity of physical activity are estimated applying two current available algorithms for ActiGraph (Choi et al., 2012; Crouter et al., 2010). The inhalation rate per minute is estimated using the participant's age, sex and weight, measured intensity of physical activity, and existing equations from the US Environmental Protection Agency (EPA) (see Supporting information) (U.S. EPA, 2009).

UFP number concentration and lung-deposited surface area measurements of DISCmini are post-processed using an algorithm developed within the EXPOsOMICS project. The algorithm removes the data recorded with malfunction (e.g., flow out of range), negative or zero values, and values with a difference of 10-fold increase or decrease in successive observations, following the procedures of Klompmaker et al. (2015) and van Nunen et al. (2017). The inhaled dose of UFP is computed combining the inhalation rate (L/min) with the personal exposures concentration (particles  $\times 10^3/\text{cm}^3$ ).

### 2.3. ExpoApp real-world measurements

To test ExpoApp, we recruited 158 adults from five European cities (Amsterdam and Utrecht- the Netherlands, Basel- Switzerland, Norwich- UK, and Torino- Italy). Participants' location, physical

New study

General

Name:

Description:

Sensors

Sensor	Enabled	Sampling rate	Encrypted	Multifile
accelerometer	<input type="checkbox"/>	<div></div>	<input type="checkbox"/>	<input type="checkbox"/>
barometer	<input type="checkbox"/>	<div></div>	<input type="checkbox"/>	<input type="checkbox"/>
gps	<input type="checkbox"/>	<div></div>	<input type="checkbox"/>	<input type="checkbox"/>
screen	<input type="checkbox"/>	<div></div>	<input type="checkbox"/>	<input type="checkbox"/>

User sensor data

Browse

Add MicroAeth

Browse

Add DiSCmini

Browse

Near-body & on-body monitors

☐

Backup

☐

Algorithms

Geo-location:

Donaire-Gonzalez et al. 2016

Acceleration-to-Actigraph counts:

Donaire-Gonzalez et al 2018

Wearing time:

Choi et al 2012

Physical Activity (METs):

Crouter et al 2010 and 2013

Inhaled Rate:

Environmental Protection Agency 2009

Green Spaces:

Triguero-Mas et al 2017

Black Carbon:

Hagler et al. 2011

DiSCmini:

Klompaker et al. 2015

Sociodemographic variables

Subject general info

Browse

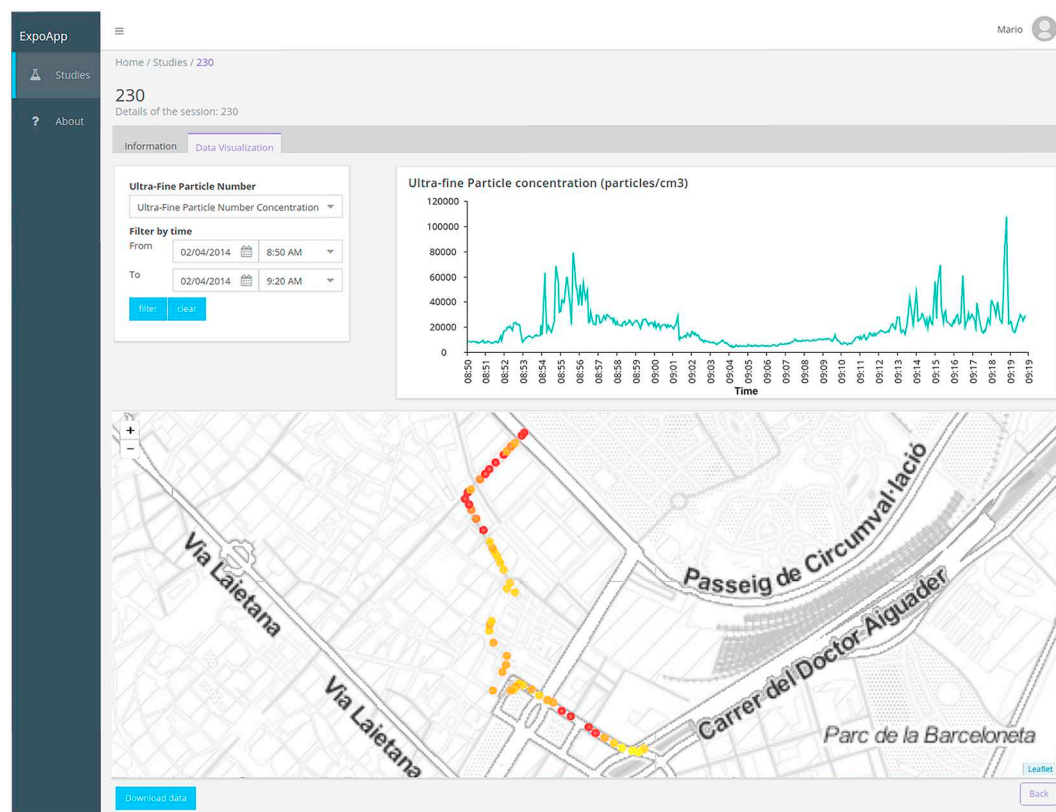
Subject geolocation info

Browse

Discard

Save

Fig. 1. Screenshot of the deployment, post-processing, and integration settings of the ExpoApp system.



**Fig. 2.** Screenshot of the interactive visualization of the spatial and temporal distribution of the ultrafine particles exposure over 24 h for one participant. Colour scale ranges from low (yellow) to high (red) UFP concentration (particles/cm<sup>3</sup>). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

activity, and exposure to UFP were monitored three times for 24 h in three different seasons over one year (2014–2015). The ethics committees of all the participating research centers approved the study, and written informed consent was obtained from all participants.

During each monitoring session, participants wore a belt (SPIbelt®) adapted to carry a smartphone running ExpoApp and a backpack adapted to carry the DiSCmini. ExpoApp was installed on a Galaxy S3 (GT-I9300, Samsung; Seoul, South Korea) smartphone (7.6 × 13.6 cm), which was supplied to each participant. ExpoApp was configured to estimate time in microenvironment (home, work, in-transit, or others) every 10 s, wearing compliance (yes/no), intensity of physical activity (METs), inhalation (L), inhaled UFP (N), and contact with green spaces (yes/no). The air inlet of the DiSCmini was equipped with an impactor and attached to one strap of the backpack in the breathing zone. The DiSCmini provides information on date, time, UFP number concentration, and lung-deposited surface area every 1 s.

## 2.4. Validation measurements

In addition, for the purpose of validation, participants also carried a GPS-Tracker and an accelerometer, attached to the same belt of the smartphone, and completed a TAD. We used the commercial GPS-tracker SCI-TK5100 (Spy Chest Inc.; Florida, USA) to assess accuracy of the geo-location measures provided by ExpoApp. The SCI-TK5100 tracker was selected because of its long battery life (60 h), reduced volume (7.6 × 4.9 × 3.6 cm), and high accuracy (2.5 m). The tracker was configured to provide information on date, time, and geographical coordinates every 10 s. The accelerometers used were the wGT3X+ (in Norwich, Torino, and Basel) and the wActiSleep+ (in Amsterdam/Utrecht) (ActiGraph; Florida, USA). These accelerometers are portable, lightweight, and small (4.6 × 3.3 × 1.5 cm) devices that record comparable acceleration measurements in the three axes. From them, we

obtained participants' wearing intervals (yes/no) and intensity of physical activity (METs) every 10 s (Choi et al., 2012; Crouter et al., 2010). The TAD was used as a reference tool to evaluate the time spent in each microenvironment. The TAD also recorded the participants' travel modes and potential operational problems with the devices.

## 2.5. Statistical analysis

Participants' characteristics are presented as n (%) for categorical variables and mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables with normal and non-normal distributions, respectively.

### 2.5.1. System reliability

To assess reliability of the system (i.e., application stability and smartphone battery life autonomy), we compared ActiGraph vs ExpoApp. As both ActiGraph and ExpoApp were attached to the same belt, differences on wearing compliance were understood as ExpoApp system failure. ActiGraph comparison was chosen over GPS-tracker because of the well-known system reliability of ActiGraph for personal monitoring and because the smartphone technology has been previously found to provide a more complete geo-location tracking of people than commercial GPS-trackers (Donaire-Gonzalez et al., 2016). We defined invalid wearing compliance as having monitored an individual's exposure for < 10 h each of the 24-hour monitoring periods following the recommendations for ambulatory assessments (Heil et al., 2012). Failure rate comparison between ExpoApp and ActiGraph was evaluated using chi-squared test.

### 2.5.2. Measurements validity

To assess the geo-location accuracy of the Galaxy S3, we estimated the distance between geo-locations taken at the same time with



ExpoApp and GPS-tracker. To assess if smartphone geo-location has a street-level accuracy (i.e. to identify in which street the participant is located), a cut-off point of 25 m was established, taking into account the properties of concomitant distance analysis (Donaire-Gonzalez et al., 2016). To assess the accuracy of time spent in each microenvironment (home, work, in-transit, and others) from ExpoApp, a misclassification matrix between the ExpoApp and TAD was generated and its corresponding classification statistics were computed. The agreement between ExpoApp and TAD was assessed using the Gwet agreement coefficient (AC1), which circumvents the known weakness of kappa (Wongpakaran et al., 2013). To assess the accuracy of ExpoApp and physical activity measurements, the agreement between the ExpoApp and ActiGraph on the average intensity from concomitant observations was assessed using the Lin's concordance correlation coefficient (CCC) (Lin, 1989). The CCC can be conceptualized as the ratio of between-subject variance to total variance. In other words, it provides a measure of the percentage of differences attributable to the participants, and its complement (1-CCC) gives the percentage of differences attributable to the method. We classified the AC1 and CCC as poor (< 40%), fair (40–59%), good (60–74%), and excellent ( $\geq 75\%$ ), following a standardized ordinal scale (Cicchetti & Guidelines, 1994). As a post-hoc analysis, we applied a city-specific acceleration-to-count equation to assess the differences between cities in terms of the fixation of the smartphone to the belt.

### 2.5.3. Participants exposure levels

Participants' exposure levels are presented as n (%) for categorical variables and mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables with normal and non-normal distributions, respectively. Finally, we used Kruskal-Wallis test to evaluate the differences in the exposure to UFP according to participants' contact with green spaces in each city. All analyses were conducted using R 3.2.2 (2015 The R Foundation for Statistical Computing).

## 3. Results

### 3.1. Participants' characteristics

Participants were on average 61 years old; 58% were male; 67% were highly educated; and mean body mass index was 25 kg/m<sup>2</sup> (Table 1).

### 3.2. System reliability

From 457 person-days measurements out of 474 possible (6 participants were monitored only ones and 5 participants were monitored only twice), 399 and 373 measurements met the minimum of 10 h of wearing time from the ActiGraph and ExpoApp, respectively. The failure rate comparison across study areas was non-significant in Amsterdam/Utrecht (p-value = 1), Torino (p-value = 0.5), and Basel (p-value = 0.4) but statistically significant in Norwich (p-value = 0.02) (Table 2).

**Table 1**

Description of participants' demographic characteristics across study areas.

Demographic characteristics	All (n = 158)	Basel (n = 48)	Norwich (n = 25)	Torino (n = 43)	Amsterdam/Utrecht (n = 42)
Age (years), mean (SD)	60.5 (6.5)	60.3 (8.5)	60.7 (4.4)	59.7 (4.6)	61.4 (6.7)
Sex, male, n (%)	91 (57.6)	23 (47.9)	11 (44.0)	22 (51.2)	35 (83.3)
Educational level <sup>a</sup> , high, n (%)	105 (66.5)	44 (91.7)	13 (52)	13 (30.2)	35 (83.3)
BMI (kg/m <sup>2</sup> ), mean (SD)	25.2 (4.1)	24.8 (4.1)	26.6 (3.6)	25.1 (4.5)	25.1 (3.8)

BMI: Body Mass Index.

<sup>a</sup> The educational level was recorded at the time of inclusion in the study and classified as high or low (high: university education or higher; low: high school or lower).

**Table 2**

Comparison of failure rate between ExpoApp and ActiGraph across study areas.

Study areas	Monitor	Failure rate (%)	p-Value
Basel (N° person-days = 137)	ActiGraph	20.5	0.389
	ExpoApp	25.6	
Norwich (N° person-days = 74)	ActiGraph	12.2	0.015
	ExpoApp	29.7	
Torino (N° person-days = 126)	ActiGraph	14.3	0.495
	ExpoApp	18.3	
Amsterdam/Utrecht (N° person-days = 120)	ActiGraph	2.5	1
	ExpoApp	3.3	

We defined failure as having monitored individuals for < 10 h of the 24-hour monitoring period.

### 3.3. Measurements validity

The geo-location agreement between the GPS-tracker and the ExpoApp showed that 74% of all ExpoApp measurements achieved accuracy at the street level (< 25 m) (Fig. 3). However, the difference between ExpoApp and GPS in Torino (median (IQR) = 21 (Hagler et al., 2011) meters) was statistically significantly higher than the one in Basel (median (IQR) = 14 (Choi et al., 2012) meters), Norwich (median (IQR) = 15 (Choi et al., 2012) meters) and Amsterdam/Utrecht (median (IQR) = 16 (Choi et al., 2012) meters).

The agreement on the time spent in each microenvironment between the TAD and the ExpoApp was found to be excellent (AC1 (95%CI) = 86.6% (86.5–86.7)) (Fig. 4). The agreement on time in each microenvironment was 88.4% (88.2–88.6) in Basel, 82.5% (82.1–82.9) in the Norwich, 88.0% (87.8–88.2) in Torino, and 85.3% (85.0–85.5) in Amsterdam/Utrecht.

The overall agreement between ActiGraph and ExpoApp on the physical activity measurements was found to be very good (CCC (95%CI) = 75.7% (71.5–79.4)) (Fig. 5). The agreement of physical activity across cities was 48.2 (39.6–56.1) in Basel; 85.2 (75.9–91.1) in Norwich; 90.1 (86.2–92.9) in Torino; and 91.6 (88.4–93.9) in Amsterdam/Utrecht. However, when applying the city-specific accelerometer-to-count conversion algorithms (Fig. S1), the overall agreement on physical activity was 89.9% (87.9–91.5) and the agreement in Basel improved from 48.2 (39.6–56.1) to 78.0 (70.7–83.7) (Fig. S2).

### 3.4. Participants' exposure levels

Based on ExpoApp, participants spent a median of 2 h in-transit per day; 25% performed  $\geq 30$  min of moderate-to-vigorous physical activity ( $\geq 3$  METs) per day; and 24% spent  $\geq 30$  min in green spaces per day. Participants were exposed to a median of UFP concentration of  $6.1 \times 10^3$  particles/cm<sup>3</sup> and inhaled a median of  $16.5 \times 10^{10}$  UFP/day (Table 3).

When comparing exposure to UFP according to participants' contact with green spaces per city (Fig. 6), there were no differences regarding UFP concentration. In contrast, there were significant differences regarding UFP inhaled dose. In addition, in the Netherlands, the differences in the inhaled dose of UFP were in the inverse direction to the rest

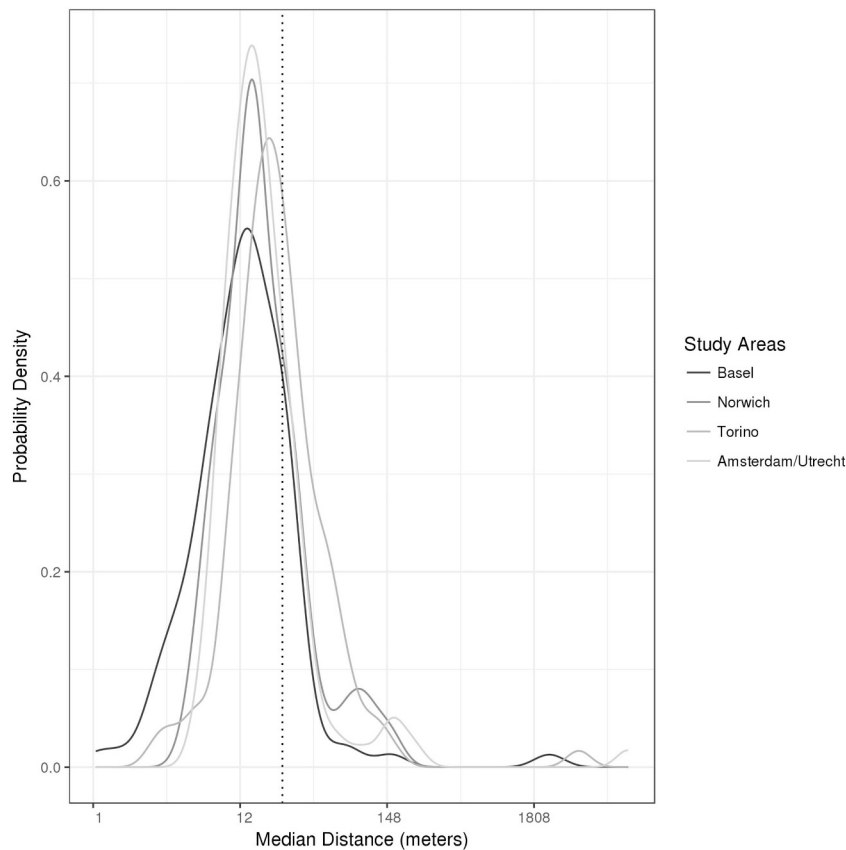


Fig. 3. Distribution of participants' median geo-location difference between the ExpoApp and GPS-tracker measurements. Dotted vertical line is 25 m.

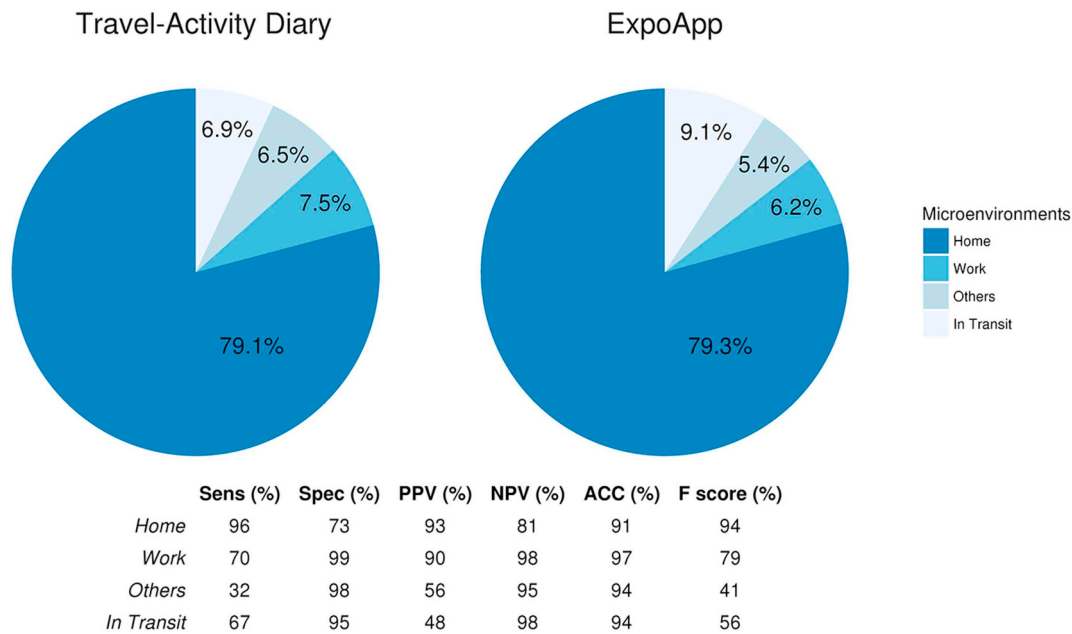
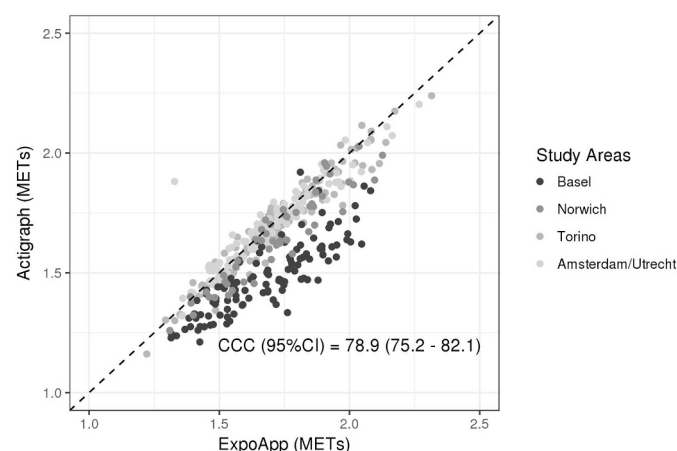


Fig. 4. Agreement between the ExpoApp and travel-activity diary time spent in microenvironments (Gwet agreement coefficient AC1 (95% CI) = 86.6% (86.5–86.7)).  
Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; ACC: Accuracy; F score: the harmonic mean between sensitivity and positive predictive value. The agreement AC1 (95%CI) in each study area was: Basel = 88.4 (88.2–88.7); Norwich = 82.5 (82.1–82.9); Torino = 88.0 (87.8–88.2); and Amsterdam/Utrecht = 85.3 (85.0–85.5).



**Fig. 5.** Comparison of person-day physical activity intensity measures (expressed in Metabolic Equivalent Task, METs) between ExpoApp and ActiGraph. The agreement CCC (95%CI) in each study area was: Basel = 48.2 (39.6–56.1); Norwich = 85.2 (75.9–91.1); Torino = 90.1 (86.2–92.9); and Amsterdam/Utrecht = 91.6 (88.4–93.9).

of the study areas, being the inhaled dose lower in those participants with greater contact with green spaces ( $p$ -value < 0.001).

#### 4. Discussion

We have presented a new flexible exposure assessment system - the ExpoApp. In a real-world panel study conducted in five European cities, we have proved the reliability of the system, the accuracy of the measurements, and the usefulness of its exposure assessment. In our study, we specifically showed ExpoApp flexibility to integrate UFP dose (particles/day), inhalation rate and contact with green spaces using a smartphone, research-grade portable monitors, free available maps, and validated equations. The reliability of the system was comparable to ActiGraph, the most commonly used accelerometer in physical activity research. The accuracy of ExpoApp measurements in time spent in microenvironments and intensity of physical activity was excellent. ExpoApp allowed us to observe that participants with more contact with green spaces had higher inhaled dose of UFP, except for the Netherlands study area where the relationship was the inverse. These differences may be attributed to differences on participants' behaviour (e.g., physical activity) and characteristics rather than their exposure level.

Reliability of the system and accuracy of geo-location and accelerometer measurements differed across cities. We suspect that these differences were mainly due to human factors. The highest failure rate was in Norwich and this is likely due to issues related to limited personnel involved in the fieldwork. The distance between geo-locations taken at the same time with the GPS-tracker and ExpoApp was above

25 m in 26% of measurements, especially in Torino. This could be explained by some intrinsic temporal error alignment in concomitant geo-location (Donaire-Gonzalez et al., 2016), participants' failure to carry both monitors as instructed, and distinctive city characteristics (Duncan et al., 2013) (i.e. Torino is characterized by a high prevalence of street canyons). However, it is worth mentioning that the differences in geo-location accuracy did not affect the estimates of time spent in microenvironments across cities. In Basel, the use of the general accelerometer-to-count conversion algorithm lead to an overestimation of the physical activity level of individuals (METs) and the lowest agreement with ActiGraph. This was due to a too tight fixation of the smartphone to the belt. As it is shown in Fig. S1, participants from Basel had smaller acceleration for the same intensity of physical activity than the rest of participants from other study areas.

#### 4.1. Comparison with previous studies

To the best of our knowledge, this is the first study that has developed and validated an integrated tool to assess multiple personal external exposures on a large scale. Therefore, ExpoApp can only be compared against other research (i.e. CalFit) and commercially-available (e.g. Moves-App, Gyroscope, and Arc) smartphone applications and wrist-worn monitors (e.g. Fitbit Surge, Apple Watch, and Microsoft Band).

The CalFit application developed by the University of California, Berkeley, records the measurements of satellite and network navigation systems and accelerometer built-in smartphone (Seto et al., 2011). CalFit also provides valid estimates of the time spent in each micro-environment and physical activity of individuals, similar to ExpoApp (Donaire-Gonzalez et al., 2016; Donaire-Gonzalez et al., 2013). However, ExpoApp shows a higher application reliability and lower battery consumption than CalFit, as measured by the comparison of the failure rates of ExpoApp (84/457 (18%)) and CalFit (11/36 (31%)) (Donaire-Gonzalez et al., 2013). Moreover, ExpoApp records the measurements of more sensors built-in the smartphone, like the barometer and screen status (turn on/off), which are useful for indoor/outdoor differentiation and phone use, respectively, and facilitates the interconnectivity with on-body and near-body sensors. Finally, the ExpoApp maximizes the data safety of participants using asymmetric encryption (128 bits) for the measurements and backing-up them into the ExpoApp Server using a secure shell protocol.

The smartphone applications (Moves-App, Gyroscope, and Arc) continuously monitor geo-location while individuals carry their phones as usual (i.e. not attached in a belt). These applications identify the microenvironments and the travel modes of individuals. From a research point of view, they are very appealing tools because they are free and, unlike ExpoApp, work on all smartphones operating systems (iOS and Android). However, to date, the validity of their microenvironmental and travel mode estimates are still untested. These smartphone-based applications also count the steps of individuals, but the accuracy of the steps counts for Moves-app has been found to be low (Case et al.,

**Table 3**  
Description of participants' exposure across study areas.

ExpoApp measures	All (n = 151)	Basel (n = 45)	Norwich (n = 25)	Torino (n = 40)	Amsterdam/Utrecht (n = 41)
Time in transit (hours), median (IQR)	2.1 (2.0)	2.8 (2.5)	2.1 (1.8)	2.5 (3.2)	1.5 (1.3)
Physical activity (METs), median (IQR)	1.34 (0.16)	1.31 (0.19)	1.33 (0.11)	1.35 (0.15)	1.35 (0.16)
Moderate-to-vigorous physical activity <sup>a</sup> , ≥ 30 min, n (%)	37 (25)	10 (22)	6 (24)	6 (15)	15 (37)
Inhalation rate (L/min), median (IQR)	8.65 (2.21)	8.50 (2.17)	9.44 (2.15)	8.62 (2.46)	8.69 (2.14)
Ultra-fine particle concentration (particles × 10 <sup>3</sup> /cm <sup>3</sup> ), median (IQR)	6.1 (3.6)	5.6 (2.9)	5 (2.2)	9.5 (3.3)	5.6 (2.7)
Inhaled ultra-fine particles, (particles × 10 <sup>10</sup> /day), median (IQR)	16.5 (11.5)	12.6 (10.2)	17.8 (15.2)	19.2 (12.6)	16.1 (9.8)
Time in green spaces, ≥ 30 min, n (%)	36 (24)	5 (11)	1 (4)	7 (18)	23 (56)

IQR: interquartile range.

<sup>a</sup> Moderate-to-vigorous physical activity (≥ 3 METs).

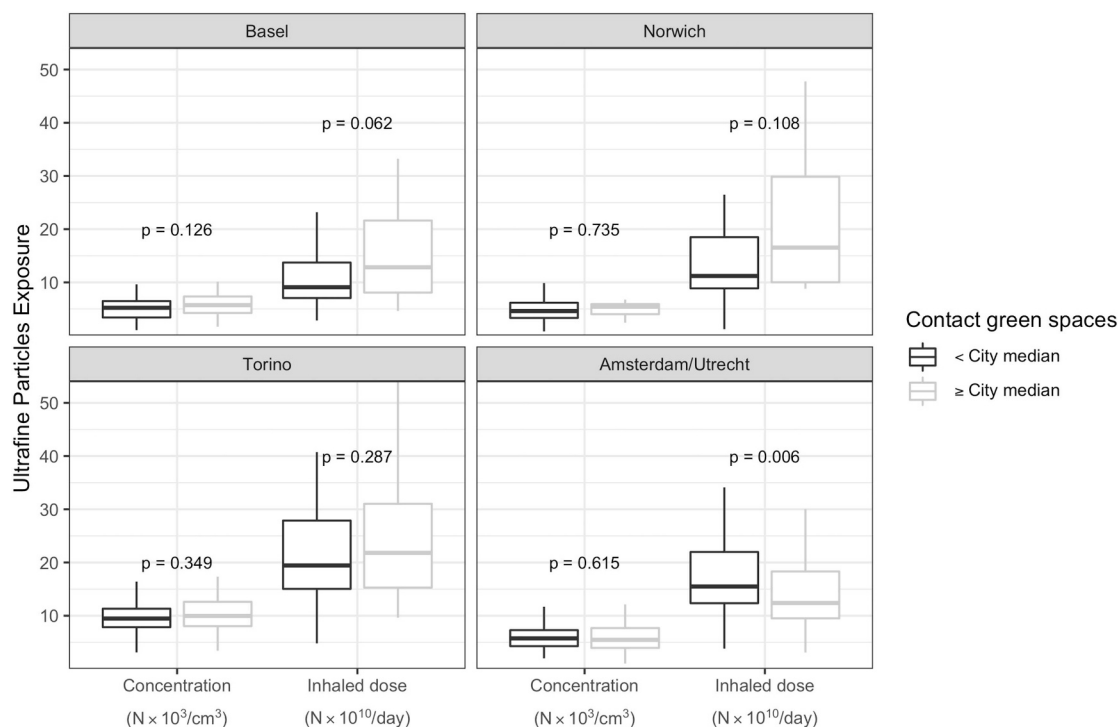


Fig. 6. Study area comparison of exposure to ultrafine particles (concentration and inhaled dose) according to participants' contact with green spaces (Kruskal-Wallis Test).

2015; Kooiman et al., 2015), possibly because of the lack of control on the way the smartphone is worn. In addition, these applications lack the interconnectivity with other sources of information (i.e. DiSCmini and OpenStreetMap), which limits their use for environmental studies.

The wrist-worn monitors like those manufactured by Fitbit, Apple or Microsoft are easy to wear, and provide valid real-time estimates of individual's heart rate (Shcherbina et al., 2017). Some of these monitors also incorporate GPS receptors or use smartphone to geo-localize these measurements. However, in comparison with ExpoApp, these monitors have several limitations. Their use is not as widespread as mobile phones, which it is a challenge to get representative samples. The battery life of these commercially-available monitors ranges from hours to weeks depending on the use. According to the company data sheets, the battery life of the Fitbit Surge 2, Apple Watch Series 4, and Microsoft Band 3 enabling GPS-tracking is 10, 6, and 4 h, respectively. Meanwhile, the battery life of ExpoApp with the current configuration is 18 h. Accessibility to the recorded data could be problematic because in some cases it would require the development of a specific software to have access to the time-resolved measurements (Shcherbina et al., 2017). Finally, but not least important, the confidentiality of the personal measurements is compromised because of the weak existing privacy laws (Board, 2014) and the ambiguous explanation provided in the privacy policy of the enterprises about the use of personal data and the impossibility to prevent this use. Despite the abovementioned limitations of these manufactured monitors, if researchers wish to include them in the exposure assessment, as long as the monitors allow the access to its time-resolved measurements, ExpoApp can interact with them through Bluetooth 4.0 protocols.

#### 4.2. Data privacy

In ExpoApp system, the privacy of participants' data is ensured by the encrypting of data in the phone, transferring them to the server using a secure shell protocol, processing them at the server without using any third party interfaces, like Google API, and therefore allowing access to the data only to researchers (Ateknea Solutions has no access),

and removing them from the server whenever the study finishes. Moreover, Ateknea privacy policy (see Supporting information) ensures that data will be only accessible to Ateknea after a researcher's request and only with the aim to solve any technical problems produced during the backing-up, post-processing, integration, visualization or interaction.

#### 4.3. Strengths and limitations

ExpoApp measurement transparency is ensured by providing researchers access to the raw and post-processed measurements, as well as the post-processing algorithms. Results therefore can be replicated and improved continuously by researchers, which may allow ExpoApp eventually to include these improvements on the system. Moreover, the currently available algorithms in ExpoApp have been developed using as 'gold standard' the available research-grade monitors in order to achieve the maximum accuracy on their estimates, which is not a common approach for mHealth applications (Kumar et al., 2013). Another strength of the study is the relatively large sample of individuals from five different cities monitored while engaged in their daily life activities, which maximizes the external validity of the present results.

However, further work is needed, particularly to systematize the way of carrying the smartphone, and thus achieve unattended, remote and reliable assessments, which are essential for large epidemiological studies. The system reliability and measurement accuracy depends on deployment factors, as demonstrated by the high failure rate observed in Norwich and physical activity results in Basel. Currently, ExpoApp Mobile is only available for Android platforms, which prevents performing systematic deployments among a representative sample of participants. The accelerometry-to-count conversion algorithm depends on the type of accelerometer built-in the smartphone, which implies that there is still a need to develop specific conversion algorithms for most smartphones. The smartphone needs to be worn on the waist attached to a belt in order to ensure the validity of the accelerometry-to-count conversion, which could be burdensome for long monitoring assessments. Wearable physical activity monitors could be integrated



into the ExpoApp system to improve physical activity assessment. This would allow participants to carry the smartphone anywhere, while maintaining the benefits of the more complete geo-location tracking provided by smartphones over commercial GPS-trackers (Donaire-Gonzalez et al., 2016). The current physical activity algorithm does not take advantage of some geographical information (e.g. the slope of the terrain and/or microenvironments) to improve its estimates for some behaviours like cycling (Maddison & Ni Mhurchu, 2009). The travel-activity algorithm does not use the barometric and accelerometry information to improve the detection of the transition between indoor and outdoor environments. ExpoApp does not have an algorithm to automatically detect the travel mode used by participants and the interaction with the free available environmental maps needs to be developed further, allowing researchers to obtain more environmental attributes from the geo-location such as surrounding facilities (e.g. proximity to restaurants, which could be a major source of UFP concentration).

#### 4.4. Applicability

ExpoApp system, thanks to its flexibility to integrate other measurements, its reliability (i.e. low failure rate), and the accuracy of its measurements, together with the current widespread use of smartphone technology worldwide, it is a feasible tool for population-based studies. In addition, the ability of ExpoApp to contextualize individuals' physical activity, as well as to characterize day-to-day mobility patterns, makes easier to disentangle the interrelationships between these exposures and individuals' health and well-being. The system can also be useful for behavioural interventional studies, such as, cardiovascular or respiratory interventions, revealing whether participants are fulfilling the intervention recommendations (e.g. volume of physical activity in green spaces).

On the other hand, the ability of ExpoApp system to integrate geo-location with other personal measurements (objective or self-reported) makes it a useful system to study different sources of exposure, quantify exposure levels and estimate the inhaled dose of air pollution. Moreover, the rapid development of low-cost personal monitors will help to scale up the sample size of these studies, making the inclusion/use of these third-party measurements more appealing for researchers (U.S. Environmental Protection Agency, n.d.; South Coast Air Quality Management District, n.d.; Spinelle et al., 2017).

Finally, because of the available environmental maps and geographic data, such as high-resolution air pollution maps (Apte et al., 2017; de Hoogh et al., 2016) and Normalized Difference Vegetation Index (NDVI) maps (Weier & Herring, n.d.), researchers can change the exposure modelling paradigm from static to dynamic, by taking into account environment, location, and activity of individuals every minute (Nieuwenhuijsen et al., 2014; de Nazelle et al., 2013; Lane et al., 2015). This exposure modelling together with the ease of deployment of ExpoApp (downloadable remotely and automatic remote data storage) makes this approach a feasible next step for environmental epidemiological studies focusing on environmental exposure and risk assessment.

#### Acknowledgements

The EXPOsOMICS Consortium includes (in alphabetic order): Andre F.S. Amaral, Toby Athersuch, Sabrina Bertineti, Marc Chadeau-Hyam, Leda Chatzi, Theo De Kok, Michaela Dijmarescu, David Donaire-Gonzalez, Almudena Espin Perez, Mario Fernandez, Claudia Galassi, Akram Ghantous, Hans Gmuender, John Gulliver, John Henderson, Zdenko Herceg, Gerard Hoek, Medea Imboden, Pooja Jain, Debbie Jarvis, Frank Kelly, Pekka Keski-Rahkonen, Jos Kleinjans, Manolis Kogevinas, Julian Krauskopf, Soterios Kyrtopoulos, David Morley, Nahid Mostafavi Montazeri, Alessio Naccarati, Tim Nawrot, Mark Nieuwenhuijsen, Georgiadis Panos, David Phillips, Michelle Plusquin, George Preston, Nicole Probst-Hensch, Andrea Ranzi, Stephen

Rappaport, Laia Font Ribeira, Lorenzo Richiardi, Susan M. Ring, Oliver Robinson, Alberto Rodriguez, Augustin Scalbert, Terrence Simmons, Martyn T. Smith, Jordi Sunyer, Sonia Tarallo, Veronique Terrasse, Ming Tsai, Erik van Nunen, Karin van Veldhoven, Roel C.H. Vermeulen, Cristina M. Villanueva, Paolo Vineis, Jelle Vlaanderen, Christopher P. Wild, Timo Wittenberger.

The study was funded by EC grants EXPOsOMICS (FP7-ENV-2012-308610) and HELIX (FP7-ENV-2012-308333).

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2019.02.054>.

#### References

- Apte, J.S., Messier, K.P., Gani, S., Brauer, M., Kirchstetter, T.W., Lunden, M.M., Marshall, J.D., Portier, C.J., Vermeulen, R.C.H., Hamburg, S.P., 2017. High-resolution air pollution mapping with Google street view cars: exploiting big data. *Environ. Sci. Technol.* 51 (12), 6999–7008. <https://doi.org/10.1021/acs.est.7b00891>.
- Board, T.E., 2014. Opinion | smartwatches and weak privacy rules. *The New York Times*. September 15.
- Case, M.A., Burwick, H.A., Volpp, K.G., Patel, M.S., 2015. Accuracy of smartphone applications and wearable devices for tracking physical activity data. *JAMA* 313 (6), 625–626. <https://doi.org/10.1001/jama.2014.17841>.
- Choi, L., Ward, S.C., Schnelle, J.F., Buchowski, M.S., 2012. Assessment of wear/nonwear time classification algorithms for triaxial accelerometer. *Med. Sci. Sports Exerc.* 44 (10), 2009–2016. <https://doi.org/10.1249/MSS.0b013e318258cb36>.
- Cicchetti, D., Guidelines, V., 1994. Criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychol. Assess.* 6 (4), 284–290. <https://doi.org/10.1037/1040-3590.6.4.284>.
- Crouter, S.E., Kuffel, E., Haas, J.D., Frongillo, E.A., Bassett Jr., D.R., 2010. Refined two-regression model for the ActiGraph accelerometer. *Med. Sci. Sports Exerc.* 42 (5), 1029–1037. <https://doi.org/10.1249/MSS.0b013e3181c37458>.
- de Hoogh, K., Gulliver, J., Donkelaar, A. van, Martin, R. V., Marshall, J. D., Bechle, M. J.; Cesaroni, G.; Pradas, M. C.; Dedele, A.; Eeftens, M.; et al. Development of West-European PM<sub>2.5</sub> and NO<sub>2</sub> land use regression models incorporating satellite-derived and chemical transport modelling data. *Environ. Res.* 2016, 151, 1–10. doi:<https://doi.org/10.1016/j.envres.2016.07.005>.
- de Nazelle, A., Seto, E., Donaire-Gonzalez, D., Mendez, M., Matamala, J., Nieuwenhuijsen, M.J., Jerrett, M., 2013. Improving estimates of air pollution exposure through ubiquitous sensing technologies. *Environ. Pollut.* 176, 92–99. <https://doi.org/10.1016/j.envpol.2012.12.032>.
- Donaire-Gonzalez, D., de Nazelle, A., Seto, E., Mendez, M., Nieuwenhuijsen, M.J., Jerrett, M., 2013. Comparison of physical activity measures using mobile phone-based CalFit and Actigraph. *J. Med. Internet Res.* 15 (6), e111. <https://doi.org/10.2196/jmir.2470>.
- Donaire-Gonzalez, D., Valentin, A., de Nazelle, A., Ambros, A., Carrasco-Turigas, G., Seto, E., Jerrett, M., Nieuwenhuijsen, M.J., 2016. Benefits of mobile phone technology for personal environmental monitoring. *JMIR mHealth uHealth* 4 (4), e126. <https://doi.org/10.2196/mhealth.5771>.
- Duncan, S., Stewart, T.I., Oliver, M., Mavoa, S., MacRae, D., Badland, H.M., Duncan, M.J., 2013. Portable global positioning system receivers: static validity and environmental conditions. *Am. J. Prev. Med.* 44 (2), e19–e29. <https://doi.org/10.1016/j.amepre.2012.10.013>.
- Hagler, G.S.W., Yelverton, T.L.B., Vedantham, R., Hansen, A.D.A., Turner, J.R., 2011. Post-processing method to reduce noise while preserving high time resolution in aethalometer real-time black carbon data. *Aerosol Air Qual. Res.* 11 (5), 539–546. <https://doi.org/10.4209/aaqr.2011.05.0055>.
- Heil, D.P., Brage, S., Rothney, M.P., 2012. Modeling physical activity outcomes from wearable monitors. *Med. Sci. Sports Exerc.* 44 (1 Suppl. 1), S50–S60. <https://doi.org/10.1249/MSS.0b013e3182399dce>.
- Khouri, M.J., Iademarco, M.F., Riley, W.T., 2016. Precision public health for the era of precision medicine. *Am. J. Prev. Med.* 50 (3), 398–401. <https://doi.org/10.1016/j.amepre.2015.08.031>.
- Klompmaker, J.O., Montagne, D.R., Meliefste, K., Hoek, G., Brunekreef, B., 2015. Spatial variation of ultrafine particles and black carbon in two cities: results from a short-term measurement campaign. *Sci. Total Environ.* 508, 266–275. <https://doi.org/10.1016/j.scitotenv.2014.11.088>.
- Kooiman, T.J.M., Dontje, M.L., Sprenger, S.R., Krijnen, W.P., van der Schans, C.P., de Groot, M., 2015. Reliability and validity of ten consumer activity trackers. *BMC Sports Sci. Med. Rehabil.* 7. <https://doi.org/10.1186/s13102-015-0018-5>.
- Kumar, S., Nilsen, W.J., Abernethy, A., Atienza, A., Patrick, K., Pavel, M., Riley, W.T., Shar, A., Spring, B., Spruijt-Metz, D., et al., 2013. Mobile health technology evaluation. *Am. J. Prev. Med.* 45 (2), 228–236. <https://doi.org/10.1016/j.amepre.2013.03.017>.
- Lane, K.J., Levy, J.I., Scammell, M.K., Patton, A.P., Durant, J.L., Mwamburi, M., Zamore, W., Brugge, D., 2015. Effect of time-activity adjustment on exposure assessment for traffic-related ultrafine particles. *J. Expo. Sci. Environ. Epidemiol.* 25 (5), 506–516. <https://doi.org/10.1038/jes.2015.11>.
- Lin, L.L., 1989. A concordance correlation coefficient to evaluate reproducibility.

- Biometrics 45 (1), 255–268.
- Maddison, R., Ni Mhurchu, C., 2009. Global positioning system: a new opportunity in physical activity measurement. *Int. J. Behav. Nutr. Phys. Act.* 6, 73. <https://doi.org/10.1186/1479-5868-6-73>.
- Nieuwenhuijsen, M.J., Donaire-Gonzalez, D., Foraster, M., Martinez, D., Cisneros, A., 2014. Using personal sensors to assess the exposome and acute health effects. *Int. J. Environ. Res. Public Health* 11 (8), 7805–7819. <https://doi.org/10.3390/ijerph110807805>.
- Nieuwenhuijsen, M.J., Donaire-Gonzalez, D., Rivas, I., de Castro, M., Cirach, M., Hoek, G., Seto, E., Jerrett, M., Sunyer, J., 2015. Variability in and agreement between modeled and personal continuously measured black carbon levels using novel smartphone and sensor technologies. *Environ. Sci. Technol.* 49 (5), 2977–2982. <https://doi.org/10.1021/es505362x>.
- Rappaport, S. M. Genetic factors are not the major causes of chronic diseases. *PLoS ONE* 2016, 11 (4). doi:<https://doi.org/10.1371/journal.pone.0154387>.
- Seto, E., Yan, P., Kuryloski, P., Bajcsy, R., Abresch, T., Henricson, E.; Han, J. Mobile Phones as Personal Environmental Sensing Platforms: Development of the CalFit System. In *The 23rd Annual Conference of the International Society of Environmental Epidemiology (ISEE)*; Environ Health Perspect: Barcelona, Spain, 2011. doi:<https://doi.org/10.1289/ehp.isee2011>.
- Shcherbina, A., Mattsson, C.M., Waggott, D., Salisbury, H., Christle, J.W., Hastie, T., Wheeler, M.T., Ashley, E.A., 2017. Accuracy in wrist-worn, sensor-based measurements of heart rate and energy expenditure in a diverse cohort. *J. Pers. Med.* 7 (2), 3. <https://doi.org/10.3390/jpm7020003>.
- South Coast Air Quality Management District. n.d. Air Quality Sensor Performance Evaluation Center (AQ-SPEC) <http://www.aqmd.gov/aq-spec/> (accessed May 27, 2017).
- Spinelle, L., Gerboles, M., Villani, M.G., Alexandre, M., Bonavitacola, F., 2017. Field calibration of a cluster of low-cost commercially available sensors for air quality monitoring. Part B: NO, CO and CO<sub>2</sub>. *Sens. Actuators B Chem.* 238, 706–715. <https://doi.org/10.1016/j.snb.2016.07.036>.
- Triguero-Mas, M.; Donaire-Gonzalez, D.; Seto, E.; Valentín, A.; Smith, G.; Martínez, D.; Carrasco-Turigas, G.; Masterson, D.; van den Berg, M.; Ambrós, A.; et al. Living close to natural outdoor environments in four European cities: adults' contact with the environments and physical activity. *Int. J. Environ. Res. Public Health* 2017, 14 (10). doi:<https://doi.org/10.3390/ijerph14101162>.
- Turner, M.C., Nieuwenhuijsen, M., Anderson, K., Balshaw, D., Cui, Y., Dunton, G., Hoppin, J.A., Koutrakis, P., Jerrett, M., 2017. Assessing the exposome with external measures: commentary on the state of the science and research recommendations. *Annu. Rev. Public Health* 38 (1), 215–239. <https://doi.org/10.1146/annurev-publhealth-082516-012802>.
- U.S. Environmental Protection Agency. n.d. Air Sensor Toolbox for Citizen Scientists, Researchers and Developers <https://www.epa.gov/air-sensor-toolbox> (accessed May 27, 2017).
- U.S. EPA. Metabolically Derived Human Ventilation Rates: A Revised Approach Based Upon Oxygen Consumption Rates (Final Report, 2009); EPA/600/R-06/129F; U.S. Environmental Protection Agency: Washington, DC, 2009.
- van Nunen, E., Vermeulen, R., Tsai, M.-Y., Probst-Hensch, N., Ineichen, A., Davey, M., Imboden, M., Ducret-Stich, R., Naccarati, A., Raffaele, D., et al., 2017. Land use regression models for ultrafine particles in six European areas. *Environ. Sci. Technol.* 51 (6), 3336–3345. <https://doi.org/10.1021/acs.est.6b05920>.
- Vineis, P., 2004. A self-fulfilling prophecy: are we underestimating the role of the environment in gene-environment interaction research? *Int. J. Epidemiol.* 33 (5), 945–946. <https://doi.org/10.1093/ije/dyh277>.
- Vineis, P.; Chadeau-Hyam, M.; Gmuender, H.; Gulliver, J.; Herceg, Z.; Kleinjans, J.; Kogevinas, M.; Kyrtopoulos, S.; Nieuwenhuijsen, M.; Phillips, D. H.; et al. The exposome in practice: design of the EXPOsOMICS Project. *Int. J. Hyg. Environ. Health* 2017, 220 (2 Pt A), 142–151. doi:<https://doi.org/10.1016/j.ijheh.2016.08.001>.
- Weier, J.; Herring, D. n.d. Measuring Vegetation (NDVI & EVI) <https://earthobservatory.nasa.gov/features/MeasuringVegetation> (accessed Dec 12, 2018).
- Wild, C.P., 2005. Complementing the genome with an “Exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol. Biomark. Prev.* 14 (8), 1847–1850. <https://doi.org/10.1158/1055-9965.EPI-05-0456>.
- Wild, C.P., 2011. Future research perspectives on environment and health: the requirement for a more expansive concept of translational cancer research. *Environ. Health* 10 (Suppl. 1), S15. <https://doi.org/10.1186/1476-069X-10-S1-S15>.
- Wongpakaran, N., Wongpakaran, T., Wedding, D., Gwet, K.L., 2013. A comparison of Cohen's Kappa and Gwet's AC1 when calculating inter-rater reliability coefficients: a study conducted with personality disorder samples. *BMC Med. Res. Methodol.* 13 (1), 61. <https://doi.org/10.1186/1471-2288-13-61>.